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EDITORIAL COMMENT

Spins and Loops

Linking Myocardial T_1 Time to Invasively-Measured Hemodynamics*

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Among the current armamentarium of cardiac imaging techniques, cardiac magnetic resonance imaging (CMR) is superior in its ability to characterize the composition of myocardial tissue. CMR has the capacity to noninvasively quantify abnormal areas of edema (1), intra- and extracellular fat (2), and fibrosis (3). This ability may permit the identification of injury at earlier stages of disease or in hearts that might otherwise be incorrectly considered normal on the basis of standard structural and functional analysis. When used in a research context, CMR can improve our understanding of the inter-relationships between myocardial tissue characteristics and cardiac function.

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Fibrosis imaging has both the most thoroughly investigated and the most widely used application of tissue characterization by CMR, specifically using late gadolinium enhancement (LGE) to identify areas of replacement fibrosis in the heart. From its origins in identifying areas of infarction in coronary disease and ischemic cardiomyopathy (4), LGE has demonstrated the ability to identify regional scar across a spectrum of cardiomyopathies (5) and to identify patients at increased risk of adverse events (6).

Not all myocardial scar is evident as the discrete regions of replacement fibrosis visualized as LGE, however. Recent investigation has increasingly focused on the use of contrast-enhanced CMR techniques to detect diffuse interstitial fibrosis, which can often be present in the absence of overt replacement scar. A variety of magnetic resonance imaging pulse sequences and analysis methods have been described, but, in general, all rely on the principle of quantifying changes in the ratio of extracellular to intracellular volume in the myocardium. Iles et al. (7) were the first to confirm that 1 such measure, post-contrast T_1 time, correlated with the degree of collagen deposition seen on endomyocardial biopsy after cardiac transplantation. This correlation with fibrosis at biopsy has subsequently been confirmed in a broader range of cardiomyopathies (8). In both cases, the majority of patients studied had no evidence of scar by standard LGE imaging.

At first pass it may seem a straightforward assumption that a change in collagen volume, as a marker of cardiac structural change, would imply alterations in cardiac function, such as an increase in passive stiffness. Although collagen quantity contributes to these changes, qualitative aspects of collagen, including the ultrastructural location of the fibers and post-translational modifications such as cross-linking, may be stronger determinants of such functional changes (9). The functional implications of collagen quantity changes, measurable by CMR, versus those of collagen quality changes, which are not, are not self-evident.

In this issue of the *Journal*, Ellims et al. (10) provide important hemodynamic evidence to support the hypothesis that diffuse fibrosis measured by CMR T_1 mapping can predict such functional changes. In this study, 20 heart transplant recipients referred for a clinically-indicated cardiac catheterization underwent same-day CMR, echocardiography, right heart catheterization, and left ventricular pressure-volume loop measurement. The key finding in this report is a strong correlation between the passive stiffness component of diastolic filling (β) and CMR measurement of diffuse fibrosis both by T_1 time and calculated extracellular volume fraction. The correlation between T_1 time and β persisted after correction for other parameters on multivariate analysis. Notably, no other clinical, hemodynamic, or echocardiographic parameter was significantly correlated with pressure-volume loop–measured passive stiffness, save for a borderline significant association with pulmonary capillary wedge pressure ($r = 0.47$, $p = 0.06$). No correlation was reported between the CMR measurements, or other parameters, and the time constant of isovolumic relaxation (τ).

This carefully performed invasive hemodynamic study is an important advance in understanding the role of diffuse fibrosis measurement as part of the evaluation of cardiac disease in establishing a link between fibrosis and passive stiffness. There are, however, some important caveats with regard to the participants studied when considering the generalizability of these results to other populations. It is possible that the qualitative aspects of collagen deposition after transplantation play less of a role than in other disease states. In addition to being limited to transplant recipients, participants in this study were relatively young (mean age 49 years), primarily male (80%), and largely asymptomatic (65%) at the time of study. As a group, these patients were normotensive and had normal right and left heart filling pressures. It is perhaps reassuring that values of β and τ measured in this study are comparable to those previously reported in patients with symptomatic heart failure and normal ejection fraction (11), indicating that the degree of

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diastolic abnormalities in the present study are within the range of interest for evaluation of other patients. Whether these findings will hold when applied to sicker, more symptomatic populations requires additional study.

The potential implications of this work, and of diffuse fibrosis quantification as a whole, are not limited to patients with clinically evident cardiovascular diseases. Recent data from a cohort of 1,231 patients enrolled in MESA (Multi-Ethnic Study of Atherosclerosis) demonstrated that both female sex and advancing age were associated with an increased burden of fibrosis using comparable CMR measures (12). These findings underscore the potential use of this technique in understanding the epidemiology of cardiovascular disease and point toward the promise of following their evolution in longitudinal studies. Although serial invasive hemodynamic studies in large populations are not possible, large multicenter cohort studies using CMR are of proven feasibility and value. Further well-conducted studies linking physiology with imaging, such as the present work by Ellims et al. (10), are needed to maximize this potential.

There is much to be gained by future work in exploring the implications of diffuse fibrosis in cardiac function. A well-validated quantitative imaging measurement that strongly correlates with invasively-measured hemodynamics would be of tremendous future value to cardiovascular epidemiology, the evaluation of patient response to therapy, and the evaluation of new therapies for cardiovascular disease.

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